Remarks

Rejection of claims 1 to 5 and 10 to 13 under 35 U.S.C. § 112, first paragraph

Claims 1 to 5 and 10 to 13 remain rejected under 35 U.S.C. § 112, first paragraph for the reasons set forth by the Examiner on pages 2 to 3 of the Office Action mailed 3/17/03. In sustaining the rejection the examiner states:

> The breadth of the claims as they relate to "Apo-2", recited only by name, is very broad since the specification includes "variants" in the definition. The term Apo-2 as defined in the specification includes naturally occurring and variant polypeptides (p. 12, lines 15-18 and p. 13, lines 13-26). According to the specification (p. 12, lines 8-18), a variant must be a biologically active Apo-2 and have at least 80% amino acid sequence identity with SEQ ID NO:1. "Biologically active" is broadly defined as the ability to modulate (stimulate or inhibit) apoptosis (page 17, lines 29-35). Because of the low sequence identity of SEQ ID NO:1 to known related receptors, it is not predictable what other sequences an Apo-2 polypeptide could have while still being "biologically active" and distinguishable from other receptors of the TNF receptor family. The only Apo-2 polypeptide disclosed has SEQ ID NO:1, and no other naturally occurring or variant receptors are disclosed.

Applicant traverses the rejection for the following reasons. Claims 1 to 5 and 10 to 13 recite functional and structural limitations by which one skilled in the art could determine and practice the method encompassed by said claims. In particular, it would not require undue experimentation for one skilled in the art using the teachings of the instant specification, and no more than routine skill, to determine whether an agonist antibody binding to an Apo-2 receptor induces apoptosis and whether the bound receptor has at least 80% identity to SEQ ID NO:1. The specification teaches that apoptosis can be measured by, for example, "cell viability assays, FACS analysis or DNA electorphoresis, all of which are known in the art." *See* specification at page 17, line 42 to p. 18, line 2. Also taught by the specification are methods of determining sequence identity. *See, e.g.,* page 13, line 27 to page 14, line 8. Accordingly, a person skilled in the art could readily determine—through routine experimentation and the information in the disclosure—whether an Apo-2 receptor expressed by mammalian cells had at least 80%

sequence identity to SEQ ID NO:1 and whether agonist antibody binding to that receptor induced apoptosis.

The Examiner asserts that because SEQ ID NO:1 has a low sequence identity to known related receptors "it is not predictable what other sequences an Apo-2 polypeptide could have while still being 'biologically active' and distinguishable from other receptors of the TNF receptor family." Applicant submits that the Examiner's observations on the general knowledge about this family of proteins is misplaced. Specifically, the teachings of the present specification provide guidance to a person of ordinary skill to select polypeptides having the characteristics of the presently claimed invention. Consequently, one skilled in the art could readily distinguish an Apo-2 polypeptide falling within the scope of claims 1 to 5 and 10 to 13 from other members of the TNF receptor family.

For the reasons set forth above, the rejection of claims 1 to 5 and 10 to 13 should be removed.

Objection to Claims 6 to 9 as being dependant upon rejected Claim 2

To advance the prosecution of the current application, the Applicant has canceled claims 6-9 by the present amendment. Accordingly, the objection to those claims is rendered moot. Applicant is not relinquishing claims to the subject matter of claims 6 to 9 and reserves the right to present such subject matter in a future application.

Rejection of claims 32 to 47 under 35 U.S.C. § 112, first paragraph

Claims 32 to 47 are rejected under 35 U.S.C. § 112, first paragraph because "the specification does not reasonably provide enablement for the [claimed] method wherein the cancer cells do not express Apo-2 receptor...." The Applicant requests withdrawal of the rejection of claims 32 to 47 in view of the amendment made to claims 32 and 40.

Additional Remarks

Applicant notes that the present application is related to, and claims the same priority date as, co-pending application U.S.S.N. 09/020,746 ("the '746 application"). The Applicant has previously submitted remarks and 131 declarations pertaining to three families of applications that in some way pertain to the Apo-2 receptor, and that appear to make a priority claim to a filing date prior to the effective filing date of the '746 application (and therefore, the effective filing date of the present application). *See* Responses and Amendments filed in the '746 application on January 22, 2003 and February 28, 2003. Applicant wishes to avoid further delay in issuance of the present application, which Applicant believes is in condition for allowance. Accordingly, Applicant is submitting, in the instant application, remarks and declarations consistent with those previously submitted for the '746 application on January 22, 2003 and February 28, 2003. The remarks are provided immediately below and the declarations are appended hereto as Exhibits A to D.

Applicant notes that the Examiner has acknowledged that U.S. Patent No. 6,072,047 is not prior art to the instant application (*See* March 17th Office Action, page5). As such, the remarks and a declaration pertaining to that patent (*See* response dated October 17, 2002 in the '746 application) are not believed necessary and are not being provided in the instant application. Regarding the '047 patent the examiner has stated in the March 17th Office Action that:

> The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent 6,072,047 is cited in IDS paper #6 and teaches an Apo-2 polypeptide called TRAIL-R of SEQ ID NO:2. This patent receives benefit of priority to 08/829,536, filed March 28, 1997, for the full-length receptor polypeptide, which is identical to SEQ ID NO:1 of the instant application with the exception that TRAIL-R has a 39 amino acid insert beginning at either position 182 or 185 of SEQ ID NO:2 of the patent, which insert occurs after amino acid 181 or 184espectively, of SEQ ID NO:1 of the instant application. However, the concept of **agonistic** antibodies does not appear until priority application 08/869,852, filed June 4, 1997, and the artisan of ordinary skill would have no motivation to practice the claimed method with an agonistic antibody based on the disclosure of the '536 application. This patent is, therefore, disqualified as prior art. As an aside, it is noted that the concept of antagonistic antibodies is taught in 08/869,852 [emphasis in original].

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Applicant has undertaken a review, using publicly available information, of patent applications that may or may not be pending before the Office, that contain disclosures that in

some way may pertain to the Apo-2 receptor, and that appear to make a priority claim to a filing date prior to the effective filing date of the instant application. In particular, Applicant has reviewed published European applications, published U.S. applications, U.S. patents and information provided by the Office in response to application status inquiries.

Pursuant to this review, Applicant has reviewed other families of patent applications that contain disclosures that address in some manner the Apo-2 receptor, albeit using different terminology, for instance "TR6", "DR5", and "Tango-63". In particular, Applicant notes that there appears to be three other families of applications that may be pending before the Office.

In an effort to resolve any potential issues that the Examiner could raise in respect to these three families of applications, Applicant respectfully submits the following arguments. Applicant also herewith provides three declarations under 37 CFR 1.131 executed by the inventor of the present application in respect of each of the three families discussed below. Applicant respectfully submits that no patent could issue on the basis of any of these families of applications which would be entitled to an effective filing date prior to that of the present application for the presented claims.

For the sake of clarity and convenience to the Examiner, copies of the applications and references referred to in the declarations are attached as exhibits to each respective declaration. Copies of the remaining applications and references discussed below are being provided as well. These applications and references are listed in the enclosed Supplemental Information Disclosure Statement and Forms 1449.

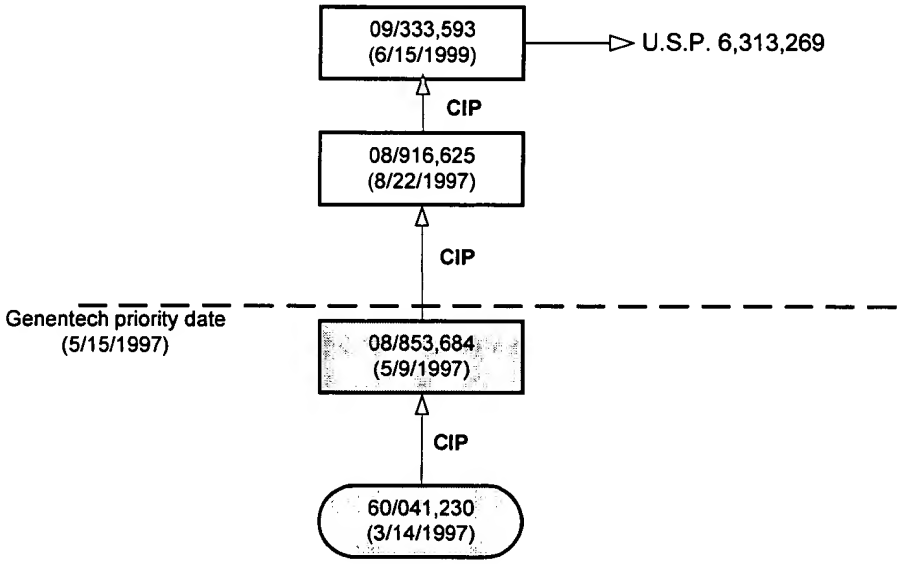
Applicant submits that the present application is in condition for allowance and should be passed to issue. If the Examiner believes that the application is not in condition for allowance or cannot be passed to issue in view of this response, Applicant respectfully requests that the Examiner contact the undersigned prior to taking any further action in this application.

Family A

The first family of applications ("Family A") consists of a series of U.S. and international applications that claim priority to U.S. provisional application number 60/041,230 (the '230 application) filed March 14, 1997. This family of applications discloses certain sequence information relating to a putative receptor the applicants term "TR6". The members of this family and the status of each such member can be summarized as follows:

- PCT/US00/16134 (the '134 application), filed on June 12, 2000 and published as WO 00/77191 on Dec. 21, 2000 [1];
- U.S.S.N. 09/333,593, filed on June 15, 1999, now U.S. Patent No. 6,313,269 ("the '269 patent");
- U.S.S.N. 08/916,625, filed on August 22, 1997, now abandoned;
- U.S.S.N. 08/853,684, filed on May 9, 1997, now abandoned; and
- U.S.S.N. 60/041,230 filed on March 14, 1997, now abandoned.

Each application filed after the (first) March 14, 1997 provisional application adds subject matter relative to its preceding family member, and as such, each is a continuation-in-part of the preceding application. The family relationships relative to the effective filing date of the present application are depicted below.



To evaluate the prior art effect of the '269 patent, or any other patent that could issue from a member of this family of applications, one must compare the specifications of each application to determine, relative to the claims of the patent, whether there is adequate support under 35 U.S.C. § 101 and § 112 for each such claim. The prior art effect under 35 U.S.C. § 102(e) of the '269 patent or any other patent arising from this family of applications relative to

[1] The public records of this PCT application show that the applicant did not designate the United States. As such, it appears that this PCT application is not a pending U.S. application.

the present application will be limited to disclosures that were filed prior to the May 15, 1997 effective filing date of the present application (i.e., only the contents of the two applications filed prior to the present application may be considered, namely, application numbers 08/853,684, filed May 9, 1997 and 60/041,230, filed on March 14, 1997).

Applicant respectfully submits that the disclosures of the '684 and '230 applications do not disclose and cannot support claims to an antibody having the characteristics of the claimed antibodies of the present application or methods of using such antibodies. It is well-settled law that a patent shall have effect under 35 U.S.C. § 102(e) as of a particular date only to the extent that there is a sufficient disclosure under 35 U.S.C. § 112, first paragraph, for the subject matter in question where the patent claims the benefit under 35 U.S.C. § 120 to an earlier filed application whose disclosure differs from that of the application giving rise to the patent. To be given effect under § 102(e), the claims of the reference patent must be supported in the manner required by 35 U.S.C. § 112 in the priority application whose date is relied on to establish the prior art status of the patent. See, *In re Wertheim*, 646 F2d 527, 209 USPQ 554 (CCPA 1981); and MPEP 2136.03, sub-heading IV.

In the present case, the applications in Family A filed prior to the effective filing date of the present application do not provide a disclosure that is sufficient under 35 U.S.C. § 101 and § 112, first paragraph, for the subject matter of the claims in the present application. Applicant notes in particular the following points:

- There is no data provided in either specification that can reasonably establish any biological function of the putative receptor. There also is no disclosure in either application identifying the ligand that binds to the putative receptor. In the context of the Tumor Necrosis Factor (TNF)-receptor superfamily, the absence of any experimental data concerning the role of the receptor or specific biological functions associated with ligand binding to the receptor render these disclosures incapable of establishing a specific, substantial and credible utility for the putative receptor, and further would render these applications insufficient to enable or providing an adequate written description of the receptor polypeptide. *See, e.g.,* paragraphs 19 and 21 of the Rule 131 declaration attached hereto as Exhibit A.

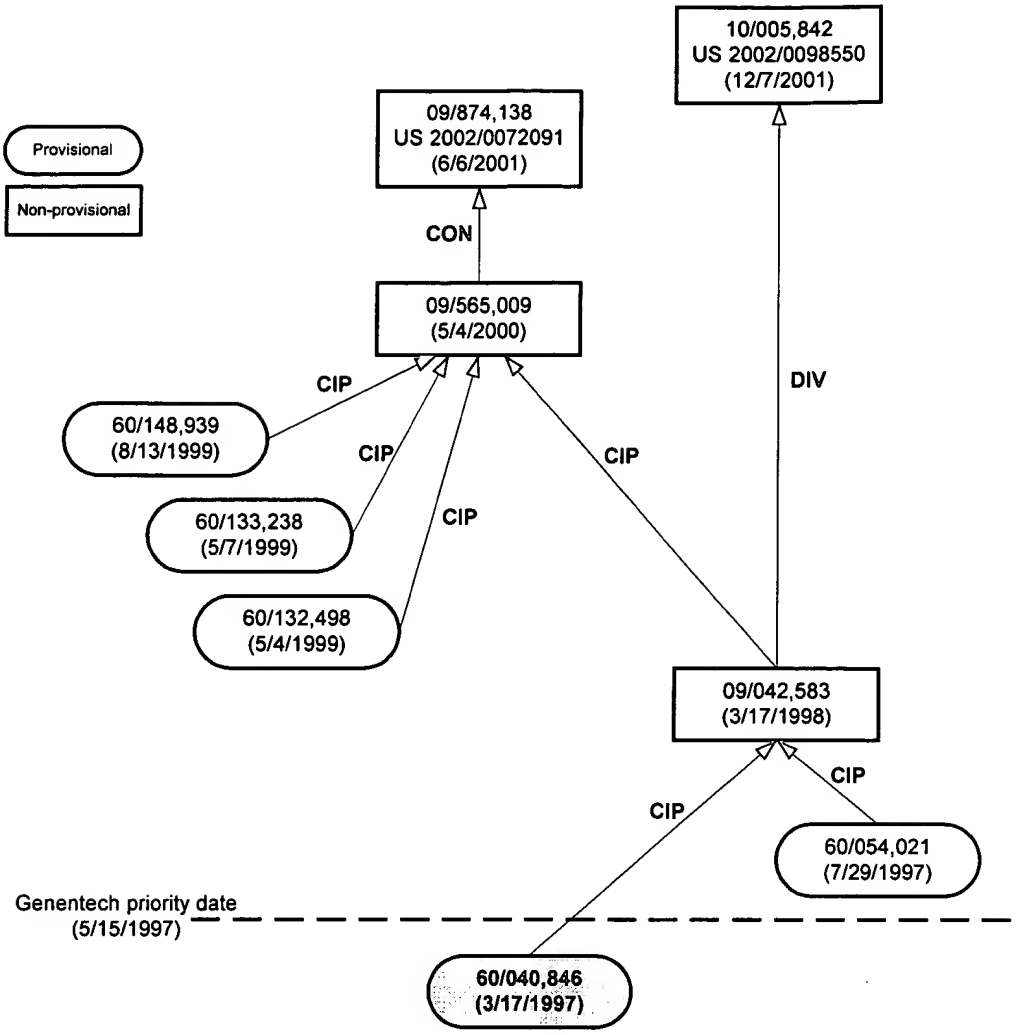
- There is no suggestion in either the '684 or the '230 application, much less a disclosure that enables and provides an adequate written description of, antibodies having the specific functions of those in the presented claims. In particular, there is

no suggestion, much less any disclosure, concerning the use of antibodies as agonists to the putative receptor. *See, e.g.*, Rule 131 declaration, paragraphs 11 and 12, of Exhibit A.

In view of these points, Applicant respectfully submits that neither the '684 nor the '230 application could meet the requirements of 35 U.S.C. § 101 or § 112, first paragraph, for a claim directed to an antibody having the characteristics of the claimed antibodies. As such, neither application could meet the requirements of 35 U.S.C. § 101 or § 112, first paragraph, for a claim directed to a method of using said antibody. The '269 patent contains no claims that correspond to antibodies or methods of using antibodies, generically or otherwise. As such, a patent issued on the basis of any application in Family A would not be prior art to the presented claims.

Family B

The second family of applications ("Family B") concerns three U.S. non-provisional applications that claim the benefit under 35 U.S.C. § 119(e) or § 120 to a series of earlier filed provisional and non-provisional applications. As depicted below, each of these applications claims, *inter alia*, the benefit under 35 U.S.C. § 119(e) to provisional application number 60/040,846 (the '846 application) filed March 17, 1997.



The '846 application is the *only* application in Family B that was filed prior to the effective filing date of the present application. As such, the prior art effect of any patent that could issue from any of the three apparently pending applications would be based upon and limited to the contents of the '846 specification. Subject matter added in the applications filed after the filing date of the '846 application would not be prior art against the present application.

Applicant has reviewed the disclosure of the '846 application. Applicant invites the Examiner to similarly review the complete disclosure of this application, and in particular, invites the Examiner to review the below-noted passages of the '846 application:

- page 5, lines 8-11 (discussing homology of the disclosed DR5 nucleotide sequence and TNFR1, FAS and DR3 as demonstrated in Figure 2) ;

- page 6, lines 28-33 discussing the degree of homology between TNFR1, FAS and DR3 and providing purported utility);

- page 9, lines 13-18 (discussing the DR5 putative death domain sequence);
- page 27, lines 3-10 (discussing purported function/utility of disclosed sequence) and lines 18-19 (discussing agonists in general);
- page 28, lines 29-31 (discussing prophetic method of screening for candidate agonist and antagonist); and
- page 29, lines 14-19 (discussing prophetic agonists as polyclonal and monoclonal antibodies).

The Examiner is also invited to review the Rule 131 declaration, attached hereto as Exhibit B, which addresses the '846 application.

As an initial point, Applicant notes that the field of the present invention concerns the superfamily of TNF receptors and ligands. Prior to the filing of the '846 application, it was appreciated in the art that the members of this superfamily possess very diverse biological functions. The '846 application confirms this understanding, stating that ligands for members of the TNF receptor superfamily are "among the most pleiotropic cytokines, inducing a large number of cellular responses, including cytotoxicity, anti-viral activity, immunoregulatory activities and the transcriptional regulation of several genes." See, '846 application, page 3, lines 15 to 17; page 3, line 37 to page 4, line 12, and page 26, lines 5 to 12. See also, Exhibit B, paragraph 15. In view of this diversity, any credible determination of a specific biological activity or function of an individual receptor member of the family would have to be based upon sufficient and unambiguous data. The '846 application does not provide such data.

Applicant notes that assertions in the '846 application concerning biological activity of the disclosed sequence are based exclusively on predictions from computer-based analyses of the sequence. The applicants of the '846 application acknowledged that their predictions were based on results obtained through data mining of human EST sequence databases. See, Pan et al., Science, 277:815-818 (1997). See also, Exhibit B, paragraph 11. Applicant also notes that the disclosure of the '846 application does not provide any experimental data concerning the actual biological function or activity of the DR5 gene or its expression product. See, Exhibit B, paragraph 16. Predictions in the '846 application concerning potential biological function or activity of the DR5 sequence or its expression product thus appear to be based solely on the results of homology analyses of the DR5 sequence to three other members of the TNF receptor superfamily. See, Exhibit B, paragraphs 12 to 14. In particular, the applicants of the '846

application speculate that the DR5 sequence encodes a death domain containing receptor, and upon this basis assert that the receptor may have a role in inducing apoptosis, despite the fact that the DR5 sequence has a very low degree of homology to the compared members of the TNF receptor superfamily (i.e., between about 17 and 30 percent).

Applicant submits that the predictions made in the '846 application of the existence of the specific biological function of induction of apoptosis upon ligand binding for a member in this family of receptors exclusively on the basis of computer-based homology analysis would not be warranted in view of the then-existing scientific understanding of this family of receptors. Applicant directs the attention of the Examiner to two literature references discussing the biological function of "death-domain" containing polypeptides that were published prior to the filing date of the '846 application. See, Rabizadeh et al., Science, 261:345-348 (1993); Chapman, FEBS Lett. 374:216-220 (1995). These references, as discussed in Exhibit B, paragraph 20, indicate that the presence of a "death domain", standing alone, cannot reasonably serve as a basis for the prediction that the receptor will induce apoptosis of a cell upon which it is expressed upon the ligand binding to the receptor. Applicant notes that these two references describe situations where the *absence* of ligand binding resulted in apoptosis in receptor members of the TNF superfamily of receptors. In other words, binding of the ligand to the receptor in these two instances turned apoptosis "off" rather than "on". In addition, Applicant submits that the low degree of homology observed in the '846 application for the putative death-domain regions relative to three other previously known TNF superfamily receptors, standing alone, would not be considered by a person of skill in the art to be a credible predictor of the specific biological function of inducing apoptosis by the polypeptide encoded by the DR5 sequence.

These factors, considered in light of the standards for evaluation of utility articulated in the PTO Utility Examination Guidelines (2001), render the '846 application incapable of establishing a specific, substantial and credible utility for claims directed to the DR5 sequence. Applicant notes that while there is no *per se* rule regarding homology based assertions of utility, the Guidelines direct Examiners to take into account both the nature and the degree of homology recited in the application. By the '846 applicants' own admission, the functions of ligands and receptors in the TNF superfamily are extremely diverse. Applicant notes that the data in the '846 application shows a very low degree of homology (no more than about 30%) of the putative DR5 receptor and three other members of this diverse superfamily. As mentioned above, the '846 application provides no experimental data regarding the function of the disclosed DR5 sequence that could serve as a basis for confirming predictions regarding the function or role of the

putative receptor. Applicant further notes that the '846 application fails to accurately identify the ligand of the putative receptor. Finally, the fact that computer homology predictions suggest that a putative receptor is likely to possess a "death domain," standing alone, cannot reasonably serve as a credible basis for predicting the specific biological function of induction of apoptosis upon ligand-binding for a member of this superfamily in view of the references cited above. In view of these considerations, Applicant submits that the '846 application does not disclose a specific, substantial and credible utility for the DR5 sequence.

The claims of the present application are directed to methods of using antibodies having particular functional characteristics (i.e., the antibodies induce apoptosis and function as agonists to the Apo-2 receptor). To support such claims, it is respectfully submitted that a disclosure would have to at least provide some data that supports the function or activity of the putative receptor and/or that would identify the ligand that binds to the putative receptor. The '846 application provides no data on either point. Instead, the '846 application simply lists potential ligands that could bind the expression product of the DR5 sequence based on information concerning ligand binding characteristics of *other* members of the TNF superfamily of receptors upon which homology comparisons are based. Applicant notes that the identity of the ligand that binds the DR5 receptor was not disclosed in this Family B of applications until the second priority application (U.S.S. N. 60/054,021) (the '021 application), which was filed after the effective filing date of the present application. The '021 application indicates that the putative DR5 receptor binds Apo-2 ligand (also termed "TRAIL"), and that this ligand *does not bind* to any of the other three TNF receptors that applicants, using homology analysis, based their predictions as to the function and activity of the putative DR5 receptor. Accordingly, the subsequent filings of this Family B of applications supports the view expressed above that the contents of the '846 application, considered alone, could not have been predictive of the actual ligand bound by the DR5 receptor, and by consequence, specific biological functions associated with ligand binding to the putative receptor.

In view of the above observations, Applicant submits that the specification of the '846 application, standing alone, could not support a claim, under § 101 and/or § 112, first paragraph, to an antibody having the characteristics of the claimed antibodies and thus for methods of using said antibodies. Applicant further notes that the effective filing date of the instant application is prior to the filing of any other application in Family B. As such, a patent issued on the basis of any application in Family B would not be prior art to the presented claims.

Family C

The third family of applications ("Family C") concerns U.S.S.N. 09/811,088, filed on Mar. 16, 2001 (hereinafter referred to as "the '088 application"). The '088 application was published as U.S. Publication No. 2002/0160446A1 last year, and claims the benefit under 35 U.S.C. § 120 to four distinct series of earlier filed non-provisional applications.[2] The members of this Family C and the status of each such member can be summarized as follows:

- *Series 1*--U.S.S.N. 09/354,809, filed Jul. 16, 1999, which is a divisional of U.S.S.N. 08/938,365, filed Sep. 26, 1997, now issued as U.S. Patent No. 5,989,909;

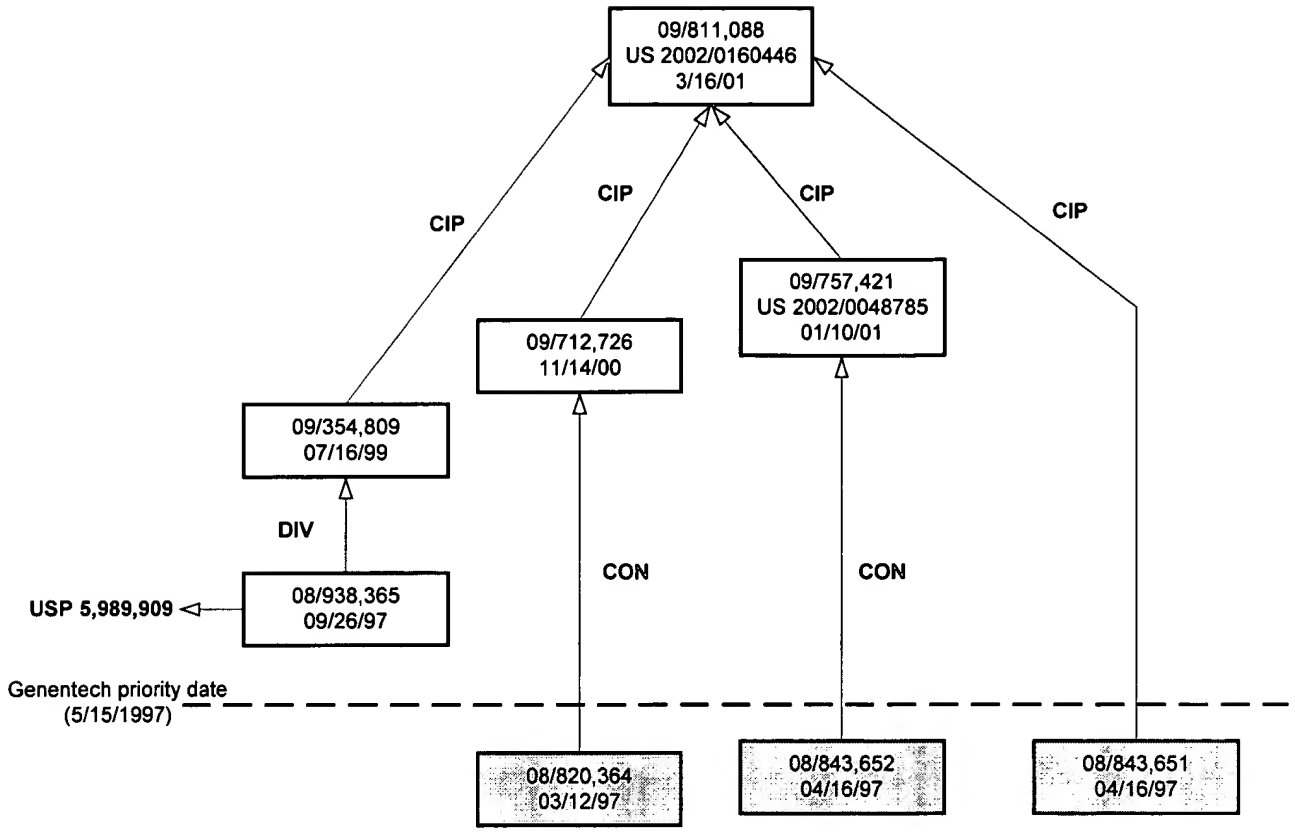
- *Series 2*--U.S.S.N. 09/712,726, filed Nov. 14, 2000, now abandoned, which is a continuation of U.S.S.N. 08/820,364, filed Mar. 12, 1997, now abandoned;

- *Series 3*--U.S.S.N. 09/757,421, filed Jan. 10, 2001, now abandoned, which is a continuation of U.S.S.N. 08/843,652, filed Apr. 16, 1997, now abandoned; and

- *Series 4*--U.S.S.N. 08/843,651, filed Apr. 16, 1997, now abandoned.

The four series of applications and their relationship to the '088 application are depicted below.

[2] An application, U.S.S.N. 09/757,421 (the '421 application) claiming priority to U.S.S.N. 08/843,652 filed April 16, 1997 directed to two forms of receptor, called "Tango-63d" and "Tango-63e", was also identified. Based on the status inquiry results, however, it is believed that the '421 application, as well as the applications to which it claims priority, has been abandoned and is no longer pending in the Office.



The first series of applications to which the '088 application claims priority (U.S.S.N. 09/354,809 and U.S.S.N. 08/938,365) were filed after the May 15, 1997 effective filing date of the present application and are directed to subject matter unrelated to the Apo-2 receptor, namely, the human gene for huchordin. Accordingly, it is believed those applications have no bearing on the prosecution of the present application.

The second series includes two applications. The first filed application in this series (i.e., U.S.S.N. 08/820,364) was filed prior to the effective filing date of the present application. The subsequent filing (U.S.S.N. 09/712,726) was a continuation of this first filed application. A review of this application reveals that it is directed to nucleic acid sequences corresponding to thymotaxin, and as such, discloses information that is unrelated to the subject matter of the present claims.

The fourth series consists of a single application (U.S.S.N. 08/842,651) that was filed prior to the effective date of the present application. This application is directed to nucleic acid sequences corresponding to "Tango-67" which is described as a soluble growth factor, and as such, discloses information that is unrelated to the subject matter of the present claims.

The third series also consists of two applications. The two applications are related to each other as parent and continuation. The first of these applications (U.S.S.N. 08/842,652; the "'652 application") was filed prior to the effective date of the present application, and it is discussed below. As indicated above (see footnote 3), it is believed that its continuation application, U.S.S.N. 09/757,421, is no longer pending in the Office. The '652 application relates to sequences termed "Tango-63".

Applicant respectfully submits that no valid patent claiming priority to the '652 application could issue with claims corresponding to the presented claims. Specifically, the '652 application does not provide a disclosure that is sufficient under 35 U.S.C. § 101 and §112, first paragraph, for the subject matter of the claims in the present application. The examiner is encouraged to review the attached declaration under 37 CFR 1.131 regarding the '652 application (Exhibit C). Additionally, the Applicant notes in particular the following points:

- The disclosure in the '652 application fails to provide any particular characterization of any domains or motifs in the putative Tango-63 receptor sequences that may constitute or act as an extracellular domain, intracellular domain or death domain. See, Exhibit C, paragraph 10. The disclosure also fails to identify any specific ligand that binds to the putative receptor. Indeed, it appears that when filed, the applicants of the '652 application were unclear whether the expression products of the Tango-63 sequences bound any ligand. See, Exhibit C, paragraph 13. In the context of the complexity of the TNF-receptor superfamily (discussed in this response above), the deficiencies in the '652 application render its disclosure insufficient to enable or provide an adequate written description.

- There is no disclosure in the '652 application of antibodies having the specific characteristics of those in the presented claims. In particular, there is no disclosure concerning agonist antibodies that mimic ligand (i.e., apoptosis-inducing) activity. *See, e.g.,* Exhibit C, paragraph 14 and 15.

In view of the above observations, Applicant respectfully submits that the specification of the '652 application, standing alone, cannot support a claim under § 101 or § 112, first paragraph, to an antibody having the characteristics of the claimed antibodies and methods of using said antibodies. As such, a patent issued on the basis of any application in Family C would not be prior art to the presented claims.

Attached please find a fourth declaration under 37 CFR 1.131 by Dr. Avi J. Ashkenazi (Exhibit D). The declaration effectively antedates the priority filing dates of the above-referenced third party applications of Families A, B, and C and is further evidence that the present application should pass to immediate issuance.

In view of the points made above and the attached declarations, Applicant respectfully requests that the Office issue the present application. As noted above, if the Examiner is not prepared to pass this application to issue, Applicant respectfully requests that the Examiner or her supervisor contact the undersigned prior to taking any further action in this application.

Respectfully submitted,
for GENENTECH, INC.

Jeffrey P. Kushan
Registration No. 43,401

Date: April 15, 2004